On page 155 (rt. col., 5 lines above page foot), the word maximum *has been added: "The maximum mean increase from baseline in systolic and diastolic blood pressures was 1.3 mm Hg and 1.6 mm Hg, respectively, for MTS and 1.6 mm Hg and 2.7 mm Hg, respectively, for OROS methylphenidate."*

A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study of Methylphenidate Transdermal System in Pediatric Patients With Attention-Deficit/Hyperactivity Disorder

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Objective: To evaluate the efficacy and safety of methylphenidate transdermal system compared with placebo, using osmotic-release oral system (OROS) methylphenidate as a reference therapy.

Method: We conducted a 7-week, randomized, double-blind, double-dummy, placebo-controlled trial in children diagnosed with attention-deficit/hyperactivity disorder by DSM-IV-TR criteria, within a community setting. The study was conducted from August 2004 to February 2005. Participants were randomly assigned to 1 of 3 treatments: methylphenidate transdermal system patch plus placebo capsule (N = 100), OROS methylphenidate capsule plus placebo patch (N = 94), or placebo capsule plus placebo patch (N = 88). Over 5 weeks, once-daily doses were optimized using 10-, 15-, 20-, and 30-mg methylphenidate transdermal system patches (9-hour wear time) or 18-, 27-, 36-, and 54-mg OROS methylphenidate capsules. Thereafter, optimal treatment doses were maintained for 2 weeks with blinded ratings of attention, behavior, and academic performance occurring at the end of each week. The primary efficacy measure was the clinician-rated ADHD Rating Scale–Version IV (ADHD-RS-IV). Additional measures included teacher, parent, and other clinician rating scales. Safety and tolerability were assessed throughout the study.

Results: The mean change from baseline in ADHD-RS-IV scores was greater for participants receiving methylphenidate transdermal system and OROS methylphenidate treatments compared with placebo ($p < .0001$). Similar results were observed for parent and teacher rating scales. More participants receiving active treatments compared with placebo were rated as improved by clinicians and parents ($p < .0001$). Adverse events were generally mild or moderate in intensity, and the most common included decreased appetite, nausea, vomiting, and insomnia.

Conclusions: The results of this study suggest that the methylphenidate transdermal system is an efficacious treatment option for children with attention-deficit/hyperactivity disorder.

Trial Registration: clinicaltrials.gov Identifier: NCT00444574

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Attention-deficit/hyperactivity disorder (ADHD) is the most common neurobehavioral disorder presenting in youth and is associated with persistently problematic symptoms of inattention, hyperactivity, and impulsivity.[1,2] Estimates of ADHD prevalence can vary among studies; however, the 2003 National Survey of Children's Health reported that ADHD affects approximately 8% of children (aged 4–17 years) in the United States.[3,4] This disorder often results in significant impairments in functioning in the academic, home, and social environments.[1,5,6] Children with ADHD are at greater risk for coexisting psychiatric problems in childhood, adolescence, and adulthood, including mood, delinquent, anxiety, and substance use disorders and low self-esteem.[6,7] Therefore, the ongoing development of safe and effective interventions is needed for the treatment of this disorder.

Evidence-based data have found that several pharmacologic treatments show consistent effects in improving the core symptoms of ADHD and associated impairments. Stimulants are the most widely studied class of medications for the treatment of ADHD and have been used for over 60 years in clinical practice.[8–10] Current guidelines recommend stimulants as first-line drug therapy for most

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children with ADHD.[11] Immediate-release stimulant formulations are rapidly absorbed and typically result in an onset of effect within 30 minutes of ingestion. Due to the short duration of effect of these medications, ranging from 3 to 6 hours, administration is generally required 2 to 3 times daily in order to maintain symptomatic improvement.[11–13] This frequent dosing can result in reduced medication compliance, compromised privacy, fear of ridicule because of in-school administration, and concerns with adequate school storage facilities for medication.[12–15] The development of extended-release oral medications, designed to resolve some of these challenges, has proven beneficial for patients who experience symptom rebound or who cannot tolerate multiple daily dosing.[14]

One such frequently prescribed extended-release methylphenidate formulation is osmotic-release oral system (OROS) methylphenidate. This once-daily oral medication was designed to maintain efficacy for up to 12 hours and uses a 22% immediate and 78% extended-release system to provide an ascending plasma profile of methylphenidate concentration through the day.[15,16]

This article reports on 1 of 2 registration trials that investigated the use of the U.S. Food and Drug Administration (FDA)–approved extended release methylphenidate transdermal system (MTS) in the treatment of ADHD. The methylphenidate transdermal system is the only non-oral medication approved specifically for the treatment of ADHD in children. The MTS consists of methylphenidate that has been solubilized in acrylic and then mixed with a polymer-based adhesive. As a result of the concentration gradient between the methylphenidate in the patch and the skin, the medication diffuses out of the patch and into the stratum corneum. A once-daily application provides continuous delivery of methylphenidate for the recommended 9-hour wear time.[17]

Previous studies conducted with MTS patch wear times ranging from 8.5 to 12 hours in children with ADHD have shown significant social and behavior improvements in recreational and classroom settings, as well as in parent ratings.[18–20] Pelham and colleagues[18,19] conducted 2 studies in children with ADHD using varying patch wear times. One of these studies utilized MTS patch sizes of 6.25, 12.5, and 25 cm^2, corresponding to dosage rates of 0.45, 0.9, and 1.8 mg/hour, respectively. MTS patches were worn for at least 12 hours per day, but could have been worn for up to 15 hours per day. Although all doses of MTS showed significant improvement from placebo in efficacy measures, loss of appetite and difficulty sleeping were experienced by many participants, presumably due to extended duration of patch wear times.[18] In the second study, a shorter MTS wear time of 8.5 hours resulted in ADHD behavioral improvement that was observed into the evening when the patch was removed at approximately 3:30 p.m. Additionally, parents reported a reduced number of side effects, including appetite loss or difficulty sleeping, when compared to the first study.[19] Based on the rates of the adverse effects in the 12- to 15-hour wear time trials, subsequent registration trials incorporated a shorter wear time of 9 hours.

MTS was approved by the FDA for the treatment of ADHD in children based on the results of 2 pivotal trials. McGough et al.[20] conducted a randomized, double-blind, placebo-controlled trial, in 80 children, that demonstrated significantly improved behavior and classroom performance with a 9-hour MTS patch wear time. Efficacy was noted from the first time point measured (2 hours after application) through to the last, at 12 hours (3 hours after patch removal), $p < .01$. During the laboratory classroom period, the most common treatment-emergent adverse events included headache, anorexia, and nausea. We report on the second pivotal trial, which is the largest MTS controlled clinical trial to date. This study utilized a naturalistic design in an outpatient population as well as a variety of clinician-, teacher-, and parent-rated measures to investigate the efficacy and safety of MTS. Naturalistic studies permit a clinical assessment of children in the settings of home and school. We evaluated the efficacy and safety of an MTS 9-hour wear time in comparison with placebo and, with reference to an established ADHD treatment (OROS methylphenidate), in a 7-week, randomized, placebo-controlled trial with > 200 pediatric participants diagnosed with ADHD.

METHOD

Participants

Children aged 6 to 12 years, inclusive, who were diagnosed with ADHD according to *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition, Text Revision (DSM-IV-TR)[2] criteria (predominantly hyperactive/impulsive, inattentive, or combined type) were eligible for study inclusion. All participants provided documentation of written assent, and all parents or legally authorized representatives signed informed consent statements after receiving thorough verbal and written descriptions of study procedures, using documents approved by each site's institutional review board prior to screening.

Participants were either naive to stimulant treatment or known to be responsive to stimulants. At screening, participants were required to have a Kaufman Brief Intelligence Test (KBIT)[21] IQ score of ≥ 80, a total score of ≥ 26 on the ADHD Rating Scale–Version IV (ADHD-RS-IV; maximum possible score of 54)[22] while unmedicated, and normal laboratory parameters and vital signs, including electrocardiogram (ECG) results. Children were excluded from enrollment if they had any comorbid psychiatric diagnosis (with the exception of oppositional defiant disorder), a history of seizures during the last 2 years, a tic disorder, or any concurrent illness or skin disorder that might compromise safety or study assessments.

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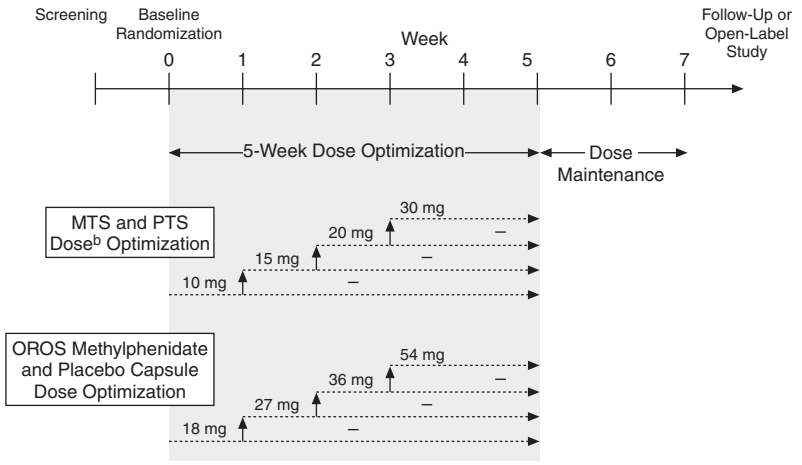
Figure 1. Study Design and Dose Titration Increments During the Dose-Optimization Phase[a]



[a]Doses could be down-titrated at certain time points as deemed necessary by the investigator based on tolerability; time points are indicated by the dashes that appear in weeks 2, 3, and 4.
[b]Based on a 9-hour wear time.
Abbreviations: MTS = methylphenidate transdermal system, OROS = osmotic-release oral system, PTS = placebo transdermal system.

Participants could not have taken clonidine, atomoxetine, antidepressants, antihypertensives, investigational medications, hepatic or cytochrome P450 enzyme altering agents, medications with central nervous system effects, sedatives, antipsychotics, or anxiolytics within the 30 days prior to study entry.

Study Design and Procedures

This was a randomized, Phase III, double-blind, multicenter, parallel-group, placebo-controlled, naturalistic home and school trial, with a lead-in dose optimization phase (Figure 1). The study was conducted from August 2004 to February 2005. Participants were enrolled and visited the study site 9 times over a 14-week period. This trial was performed in accordance with the International Conference on Harmonization Guidelines for Good Clinical Practice (1996).

Following a 2-week screening period and up to 28 days of medication washout (if applicable), participants entered a 5-week, double-blind, double-dummy dose optimization phase in which their treatments were optimized to 1 of 4 total daily dosage strengths of MTS/PTS (placebo transdermal system) or OROS methylphenidate/placebo capsules. At the first dose optimization (baseline) visit, the investigator used a computer-generated random-numbers schedule to randomly assign participants, in a 1:1:1 ratio, to receive MTS plus placebo capsule, OROS methylphenidate plus placebo patch, or placebo capsule plus placebo patch in a double-blind fashion. All participants received both a patch and capsule to be administered each day, and all were initiated on the 10 mg/9 hour MTS/PTS patch and the 18 mg OROS methylphenidate/placebo capsule dosage strength. The OROS methylphenidate/placebo tablets were encapsulated to blind the identity of the capsule's content. At the baseline visit, participants received a 1-week supply of study medication and were instructed to begin using it the following morning. Treatments were administered at approximately 7:00 a.m. each morning; patches were applied to the hip area and worn for approximately 9 hours daily (removed at 4:00 p.m.). A new patch was applied each morning, alternating hip sides so that the MTS/PTS was not applied to the same side or application site for 2 consecutive days.

After 1 week (7 ± 2 days), participants were evaluated for efficacy and tolerability. Participant response to treatment was classified by the investigator as intolerable (unacceptable safety profile), ineffective (< 25% change in ADHD-RS-IV score with an acceptable safety profile), or acceptable (at least 25% reduction in symptoms with minimal side effects). An intolerable condition required tapering the participant to a lower patch or capsule dosage strength. An ineffective condition required increasing the patch or capsule dosage strength to the next available strength. An acceptable condition required maintaining the participant on the current dose for the remainder of the study unless, in the investigator's opinion, additional symptom reduction could occur with further titration. Titration to the next largest patch or capsule dosage strength was permitted after a minimum of 1 week of using the current treatment, based on overall participant response. In addition, tapering to a lower patch or capsule dosage strength was permitted after 1 week at a given dose level, but if this occurred, no further titration was permitted. Participants who did not reach an acceptable condition by the final dose optimization visit (week 5) were withdrawn from the study.

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Participants who reached an acceptable condition by the final dose optimization visit entered a 2-week dose maintenance phase, during which they remained on their optimal dose. Evaluations for effectiveness and safety were performed at the end of each week. At the final study site visit, participants who completed at least 5 weeks of the study were given the option to enroll in an open-label extension study. Participants who chose not to enroll were followed for 30 ± 2 days to monitor safety following their last dose of study medication.

During the dose optimization and dose maintenance periods, study medication was provided to parents in bottles and individually sealed trays containing the transdermal patches for the coming week. Compliance with study medication was assessed by the weekly return of unused patches and capsules and was defined as use of between 80% and 100% of the patches and capsules dispensed.

Efficacy Measures

During the screening visit, a diagnosis of ADHD was established by a clinician on the basis of a standard psychiatric interview using the DSM-IV-TR.[2] The clinician also assessed for current and past episodes of psychopathology using the Schedule for Affective Disorders and Schizophrenia for School-Age Children: Present and Lifetime Version (K-SADS-PL)[23] diagnostic interview. The KBIT was used to assess intelligence and was administered by a trained staff member.

The primary efficacy measure was the change in ADHD-RS-IV total score at endpoint. The ADHD-RS-IV was assessed by the clinician at baseline and each study visit. The main secondary outcome measure was the Conners' Teacher Rating Scale-Revised: Short Form (CTRS-R).[24] Teachers evaluated participants using the CTRS-R (~ 10:00 a.m. and 2:00 p.m.) on 2 days each week, at least 48 hours apart, throughout the study. Other secondary outcome measures used to evaluate global impressions of ADHD severity and improvement by clinicians and parents throughout the study included the Conners' Parent Rating Scale-Revised: Short Form (CPRS-R),[24] the Clinical Global Impressions-Severity of Illness and -Improvement scales (CGI-S and CGI-I),[25] and the Parent Global Assessment (PGA), a variation of the CGI-S and CGI-I designed to capture parent/caregiver opinions of their child's disease severity and improvement from baseline (scored from 1 to 7: 1 = marked improvement, 4 = no change from baseline, 7 = marked deterioration). Using the CPRS-R, parents evaluated their child's behavior at approximately 11:00 a.m. and 3:00 p.m. on the last weekend day prior to each visit beginning with the baseline visit and at each subsequent study site visit.

Safety Measures

Safety was monitored primarily through the occurrence of spontaneously reported treatment-emergent adverse events. The investigator categorized all adverse events according to intensity (mild, moderate, or severe) and relationship to study medication (unrelated, possibly related, or probably related). Vital sign measurements (systolic and diastolic blood pressures, pulse, oral temperature, and sitting respiratory rate) were performed at screening and at all study visits. The investigator determined the clinical significance of any vital sign measurement that was outside of the normal range. Clinically significant deviations from those measurements recorded at screening were reported as an adverse event. Other safety parameters included a physical examination and height measurement at screening, body weight measurements at all visits, and laboratory measures at screening and final visit. Reference ranges for clinical laboratory measures were supplied by Covance Central Laboratory Services (Leeds, United Kingdom) and were used to assess clinical significance. In addition, a 12-lead ECG was performed at screening, baseline, the final dose optimization visit, and the final study visit or early termination. ECGs were analyzed by Covance Central Diagnostics Inc. (Leeds, United Kingdom), and the investigator determined, based on normal ranges, whether the ECG was normal, abnormal but not clinically significant, or abnormal and clinically significant. All adverse events were coded using the MedDRA (version 7.0) adverse event dictionary.

Sleep-related behaviors were evaluated starting at baseline and for all study visits using the Children's Sleep Habits Questionnaire (CSHQ).[26] The CSHQ is a 33-item questionnaire that assesses sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, and daytime dysfunction in children. Bedtime, total sleep time, nightly waking periods, and waking time are also recorded. Items are scored from 1 (rarely occurring) to 3 (usually occurring), so that total scores range from 33 to 99. Parents/caregivers completed the CSHQ on the basis of the child's sleep habits over the past week and were able to report if the items were a problem for the child.

Beginning with the first dose optimization visit, both current and prior patch application sites were assessed each week by the clinician for evidence of irritation and primary skin reactions, experience of discomfort, and transdermal system adhesion. Observations were recorded on skin evaluation scales that rated irritation, discomfort, and the adhesive performance of the patch. The dermal response scale was scored from 0 to 7 (0 = no evidence of irritation; 1 = minimal erythema, barely perceptible; 2 = definite erythema, readily visible: minimal edema or minimal papular response; 3 = erythema and papules; 4 = definite edema; 5 = erythema, edema, and papules; 6 = vesicular eruption; and 7 = strong reaction spreading beyond test site). The dermal discomfort scale was scored from 0 to 3 (0 = no discomfort; 1 = mild discomfort; 2 = moderate but tolerable discomfort; and 3 = severe, intolerable discomfort). The transdermal system adhesion

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scale was scored from 0 to 4 (0: ≥ 90% adhered—essentially no lift off of the skin; 1: ≥ 75% to < 90% adhered—some edges only lifting off of the skin; 2: ≥ 50% to < 75% adhered—less than half of the system lifting off of the skin; 3: < 50% adhered but not detached—more than half the system lifting off of the skin without falling off; and 4: MTS detached—system completely off the skin).

Pharmacokinetic Assessment

During 1 of the last 3 visits, three 3-mL venous blood samples were collected from participants at 7.5, 9, and 10.5 hours postdose for measurement of plasma *d*-methylphenidate and *l*-methylphenidate concentrations. Samples were drawn into ethylenediaminetetraacetic acid (EDTA) Vacutainer tubes (Becton, Dickinson and Company; Franklin Lakes, N.J.), and immediately after collection, the tube was placed in a refrigerated centrifuge, ice bath, or cryoblock. Within 15 minutes of collection, the chilled blood samples were centrifuged at 3000 rpm for 10 minutes. Plasma samples were stored between –10°C to –30°C immediately after separation. Plasma samples were analyzed for *d*-methylphenidate and *l*-methylphenidate using a validated chiral liquid chromatography with tandem mass spectrometry (LS/MS/MS) assay (Covance Bioanalytical Services, LLC; Leeds, United Kingdom).

Statistical Methods

Participants who were randomized and received at least 1 dose of investigational medication and had a baseline primary efficacy assessment and at least 1 postbaseline primary efficacy assessment were included in the intent-to-treat (ITT) population. The efficacy analyses were performed using the ITT population. The safety population was defined as all participants who received at least 1 dose of any investigational medication used during the study. All safety summaries were performed on the safety population. For outcome analyses, study endpoint was defined as the last postbaseline assessment for which a valid score was obtained, carried forward.

Assuming an effect size of approximately 0.5 (based upon previous studies) compared to placebo in children with ADHD, 258 participants were needed to obtain 90% statistical power at the 5% significance level. Statistical analyses were performed using SAS Version 8.2 (SAS Institute; Cary, N.C.; 2001). The primary efficacy variable was the least squares mean change from baseline to study endpoint in ADHD-RS-IV total scores and was assessed using analysis of covariance (ANCOVA) with treatment as a factor and baseline ADHD-RS-IV score as a covariate. The null hypothesis was that there was no difference between MTS and placebo. Analysis was carried out separately for comparison between MTS and placebo, and OROS methylphenidate and placebo. An analysis of the difference in change from baseline between MTS and OROS methylphenidate was also performed; however, this study was not powered to specifically detect any differences between MTS and OROS methylphenidate. A similar analysis was used for CTRS-R and CPRS-R least squares mean change from baseline to endpoint. CPRS-R total scores were analyzed using the mean of scores at the 11:00 a.m. and 3:00 p.m. time points. Additionally, mean change from baseline in CPRS-R score was calculated for the 11:00 a.m. and 3:00 p.m. time points separately, using the same ANCOVA model. CGI-I and PGA scores were analyzed using the χ^2 test. Prior to the analysis, these variables were dichotomized into 2 categories, with "very much improved" and "much improved" in 1 category considered improved and the remaining levels (minimally improved, no change, minimally worse, much worse, and very much worse) in the other.

RESULTS

Of 282 patients randomly assigned to treatment, 270 had at least 1 primary efficacy assessment and were included in the ITT population: 96 in the MTS group, 89 in the OROS methylphenidate group, and 85 in the placebo group. Reasons for withdrawal are summarized in Figure 2. Mean compliance during the dose optimization period was 98% for both the MTS and OROS methylphenidate groups and 97% for the placebo group. By the end of the dose optimization period, most participants were receiving the higher dosage strengths of MTS 20 mg or 30 mg and OROS methylphenidate 36 mg or 54 mg (Table 1). During the dose maintenance period, mean compliance was 99%, 98%, and 97% for the MTS, OROS methylphenidate, and placebo groups, respectively. During the study, mean (SD) patch wear time ranged from 8.70 (0.51) hours to 9.46 (0.53) hours.

Within the randomized population, treatment groups were similar with respect to most pretreatment and demographic characteristics, with the exception of prior ADHD medication use, which was slightly higher in the MTS group compared with the OROS methylphenidate and placebo groups (Table 2). For all subjects enrolled, the mean (SD) age, height, and weight were 8.8 (1.94) years, 53.1 (5.17) inches, and 71.6 (21.60) lb, respectively. At baseline, all treatment groups were similar with respect to ADHD symptoms as measured by ADHD-RS-IV mean scores.

Primary Efficacy: ADHD-RS-IV Total Score

As shown in Figure 3, ADHD-RS-IV mean total scores were fairly severe and similar between MTS, OROS methylphenidate, and placebo at baseline (43.0, 43.8, and 41.9, respectively), but not at endpoint (18.8, 21.8, and 32.1, respectively). Compared with placebo, both active treatment groups showed significant improvements in the change in ADHD-RS-IV mean total scores from baseline to study endpoint ($p < .0001$). The average magnitude of

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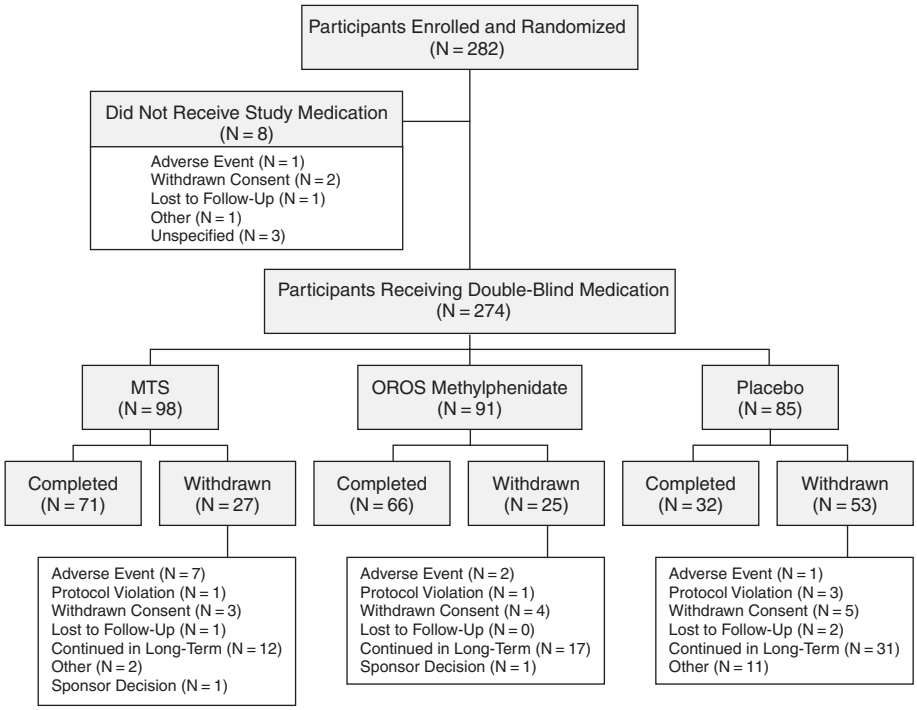
Figure 2. Disposition of Participants in a Randomized, Double-Blinded, Double-Dummy, Placebo-Controlled Phase III Trial Evaluating the Efficacy and Tolerability of Methylphenidate Transdermal System, With Reference to OROS Methylphenidate, in the Treatment of Pediatric ADHD



Abbreviations: ADHD = attention-deficit/hyperactivity disorder, MTS = methylphenidate transdermal system, OROS = osmotic-release oral system.

Table 1. Optimal Dose Distribution at Week 5, by Patch and Capsule Dosage Strength

Patch/Capsule Dosage		Treatment Group, % of Participants		
MTS (mg/9 h)	OROS Methylphenidate (mg)	MTS	OROS Methylphenidate	Placebo
10	18	7.9	4.4	0
15	27	21.1	19.1	16.7
20	36	34.2	32.4	16.7
30	54	36.8	44.1	66.7

Abbreviations: MTS = methylphenidate transdermal system, OROS = osmotic-release oral system.

changes from baseline to study endpoint was roughly a 2-fold greater improvement of ADHD symptoms in active treatments than in placebo. There was no significant difference in least squares mean change from baseline between MTS and OROS methylphenidate, p = .2192 (difference = –2.574; 95% CI = –6.690 to 1.541).

CTRS-R and CPRS-R

MTS and OROS methylphenidate treatment groups showed greater improvements over placebo in CTRS-R mean total scores from baseline to endpoint (Table 3). The least squares mean change in the CTRS-R total score from baseline to endpoint in participants treated with MTS and OROS methylphenidate was significantly different from participants treated with placebo (p < .0001) but not from each other, p = .3600 (difference = 2.231; 95% CI = –2.562 to 7.024). Similar results were seen in CPRS-R mean total scores at the morning and afternoon time periods. There was no difference observed between MTS and OROS methylphenidate treatment at 11:00 a.m., p = .2528 (difference = –3.455; 95% CI = –9.393 to 2.482), or at 3:00 p.m., p = .0864 (difference = –5.353; 95% CI = –11.478 to 0.772).

CGI-I and PGA Scales

At study endpoint, a significantly greater proportion of participants treated with MTS (N = 69, 71.9%) or OROS methylphenidate (N = 59, 66.3%) were rated as improved using the clinician-rated CGI-I, compared with placebo (N = 20, 23.5%), p < .0001. Similarly, a significantly greater proportion of participants treated with either MTS (N = 67, 69.8%) or OROS methylphenidate (N = 54, 60.7%) were rated as improved using the parent-rated PGA scale, compared with placebo (N = 21, 24.7%), p < .0001.

Pharmacokinetics

Mean plasma *d*-methylphenidate and *l*-methylphenidate concentrations were higher for MTS dosages of 10, 15, 20, and 30 mg, compared with OROS methylphenidate dos-

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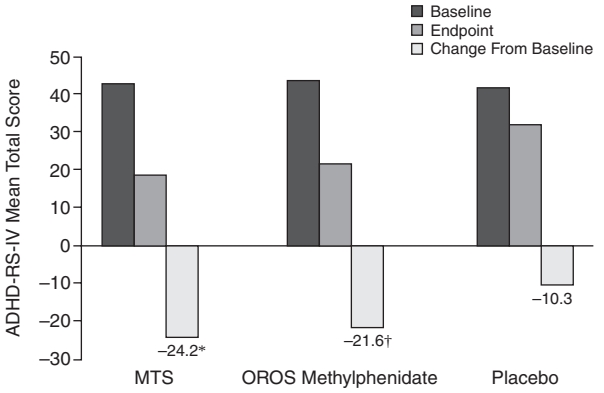
Table 2. Participant Demographics and Baseline Characteristics, All Enrolled Participants

Characteristic	MTS (N = 100)	OROS Methylphenidate (N = 94)	Placebo (N = 88)
Age, mean (SD), y	8.9 (1.96)	8.8 (1.94)	8.5 (1.91)
Age category, N (%)			
6–9 y	61 (61.0)	60 (63.8)	62 (70.5)
10–12 y	39 (39.0)	34 (36.2)	26 (29.5)
Male, N (%)	60 (60.0)	62 (66.0)	65 (73.9)
Female, N (%)	40 (40.0)	32 (34.0)	23 (26.1)
Hispanic or Latino ethnicity, N (%)	16 (16.0)	11 (11.7)	8 (9.1)
Race, N (%)			
White	79 (79.0)	75 (79.8)	64 (72.7)
Black/African American	11 (11.0)	13 (13.8)	17 (19.3)
Asian	2 (2.0)	0 (0.0)	0 (0.0)
Other	8 (8.0)	6 (6.4)	7 (8.0)
Weight, mean (SD), lb	72.9 (24.09)	73.0 (20.89)	68.7 (19.18)
Height, mean (SD), in	53.4 (5.39)	53.2 (4.97)	52.4 (5.14)
ADHD duration,[a] mean (SD), y	1.67 (2.438)	1.78 (2.377)	1.45 (1.973)
ADHD subtype, N (%)			
Combined	84 (84)	81 (86.2)	62 (70.5)
Inattentive	15 (15.0)	10 (10.6)	23 (26.1)
Hyperactive/impulsive	1 (1.0)	2 (2.1)	1 (1.1)
Unclassified	0 (0)	1 (1.1)	2 (2.3)
Prior medication use, %[b]	18	13	12

[a]Time since diagnosis of ADHD.
[b]Percentage of participants who had received or were taking ≥ 1 medication to treat ADHD prior to screening.
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, MTS = methylphenidate transdermal system, OROS = osmotic-release oral system.

Figure 3. ADHD-RS-IV Mean Total Scores at Baseline and Study Endpoint and Least Squares (LS) Mean Change From Baseline to Study Endpoint in the Intent-to-Treat Population[a]



[a]A decrease in score indicates improvement. LS means from analysis of covariance model with term for treatment as a factor and baseline score as a covariate.
*p < .0001 versus placebo, (difference = –13.893; 95% CI = –18.062 to –9.724).
†p < .0001 versus placebo, (difference = –11.319; 95% CI = –15.579 to –7.059).
Abbreviations: ADHD-RS-IV = ADHD Rating Scale–Version IV, MTS = methylphenidate transdermal system, OROS = osmotic-release oral system.

ages of 18, 27, 36, and 54 mg at the 7.5, 9, and 10.5 hours postdose time points measured. Mean plasma concentrations taken at the 9-hour postdose time point are presented in Figure 4. The higher concentrations of *d*-methylphenidate and *l*-methylphenidate observed after 9 hours of wear time for MTS and 9 hours after dosing for OROS methylphenidate suggest that the systemic exposure to methylphenidate is greater in the later part of the day with MTS treatment than with OROS methylphenidate treatment.

Safety

A total of 573 treatment-emergent adverse events were reported; of these, 505 were recorded during dose optimization and 68 were recorded during dose maintenance. The majority (99%) of the treatment-emergent adverse events recorded were classified as either mild or moderate in intensity. The most commonly reported treatment-emergent adverse events included decreased appetite, nausea, vomiting, and insomnia (Table 4). Although the absolute number of reported adverse events was higher for those receiving MTS for the 10 most common adverse events, the study was not powered to compare MTS with OROS methylphenidate, and a post hoc analysis found the difference to be statistically insignificant. Of participants randomly assigned to MTS, OROS methylphenidate, and placebo, 7.1%, 2.2%, and 1.2%, respectively, discontinued the study due to adverse events. All adverse events that led to discontinuation were consistent with typical childhood illnesses or with the known adverse events of methylphenidate and transdermal system application. In the MTS group, the adverse events leading to discontinuation were facial tics, application site erythema, application site reaction, headaches, viral infection, infectious mononucleosis, crying, irritability, and confusional state; in the OROS methylphenidate group, these included syncope, abdominal pain, anger, aggression, and headache; and in the placebo group, the reported adverse event of worsening ADHD symptoms led to discontinuation. No serious adverse events, including deaths and suicides, were reported.

No clinically significant changes from baseline or changes in the pattern in the occurrence of abnormal values in hematology, chemistry assays, or urinalysis were noted across treatment groups. Generally, there were no clinically significant effects on vital signs; however, there was a small increase in mean change from baseline in systolic and diastolic blood pressure at several visits in both active treatment groups compared with the placebo group. The maximum mean increase from baseline in systolic and diastolic blood pressures was 1.3 mm Hg and 1.6 mm Hg, respectively, for MTS and 1.6 mm Hg and 2.7 mm Hg, respectively, for OROS methylphenidate. At all postbaseline visits, both the MTS and OROS

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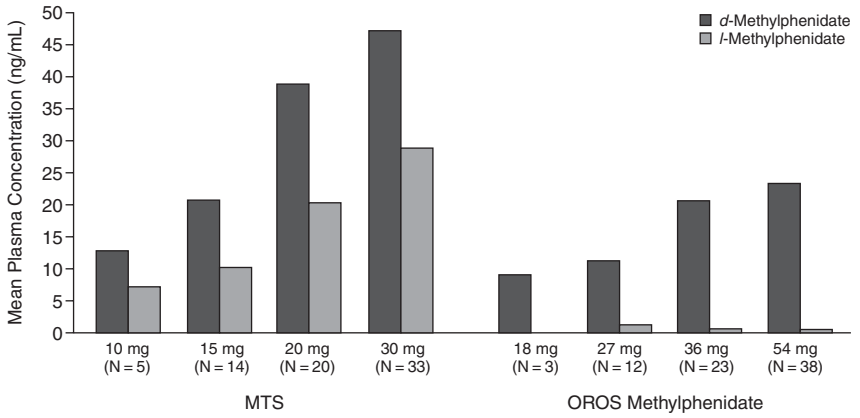
Table 3. CTRS-R and CPRS-R Mean Total Scores and Least Squares (LS) Mean Change From Baseline to Study Endpoint, ITT Population

Main Secondary Outcome Measure	Total Score, Mean (SD)		LS Mean Change (SE)	Difference (95% CI)	p Value[a]
	Baseline	Endpoint			
CTRS-R					
MTS	34.9 (18.97)	19.4 (18.50)	–15.3 (1.69)	–10.186 (–15.028 to –5.345)	< .0001
OROS methylphenidate	34.9 (18.89)	18.3 (17.44)	–17.5 (1.75)	–12.417 (–17.350 to –7.484)	< .0001
Placebo	39.1 (18.79)	31.6 (20.07)	–5.1 (1.78)	…	…
CPRS-R at 11 a.m.					
MTS	52.6 (15.43)	24.6 (21.37)	–27.0 (2.12)	–12.710 (–18.817 to –6.602)	.0001
OROS methylphenidate	51.2 (15.31)	28.4 (21.07)	–23.5 (2.14)	–9.255 (–15.384 to –3.125)	.0032
Placebo	49.6 (16.77)	37.0 (23.39)	–14.2 (2.26)	…	…
CPRS-R at 3 p.m.					
MTS	53.7 (16.69)	24.1 (20.08)	–27.4 (2.16)	–12.360 (–18.562 to –6.157)	.0001
OROS methylphenidate	51.4 (17.27)	29.1 (20.78)	–22.0 (2.23)	–7.007 (–13.283 to –0.730)	.0288
Placebo	49.8 (17.62)	37.7 (23.50)	–15.0 (2.28)	…	…

[a]Comparisons are between the LS mean change scores in the respective treatment arms and placebo. LS means from analysis of covariance model with term for treatment as a factor and baseline score as a covariate. A decrease in score indicates improvement.
Abbreviations: CPRS-R = Conners' Parent Rating Scale-Revised: Short Form, CTRS-R = Conners' Teacher Rating Scale-Revised: Short Form, ITT = intent-to-treat, MTS = methylphenidate transdermal system, OROS = osmotic-release oral system.

Figure 4. Mean 9-Hour Plasma *d*-Methylphenidate and *l*-Methylphenidate Concentrations for MTS and OROS Methylphenidate



Abbreviations: MTS = methylphenidate transdermal system, OROS = osmotic-release oral system.

methylphenidate groups were noted to have a mean decrease in weight of 2.2 and 2.1 lb, respectively, from baseline, while subjects in the placebo group had a mean increase in weight of 2.1 lb from baseline.

No clinically significant mean changes from baseline were noted for QT, QRS, PR, or RR intervals or heart rate in the MTS group. One subject in each of the 3 treatment groups had a > 60-msec increase from baseline in QT or QTc. Overall, no clinically relevant abnormal ECG results were recorded as a result of treatment.

There was little change in children's sleep habits as evidenced by the CSHQ total score and the number of sleep problems identified. CSHQ mean total scores were similar between all treatment groups at baseline, with a slightly greater mean change from baseline to study endpoint in the MTS group (–3.9 ± 6.53) compared with the OROS methylphenidate (–3.0 ± 7.75) and placebo (–3.2 ± 5.55) groups.

The highest score observed on the dermal response scale was 4 (definite edema; N = 4) in the MTS group, 5 (erythema, edema, and papules; N = 1) in the OROS methylphenidate group, and 3 (erythema and papules; N = 2) in the placebo group. All participants reporting the highest dermal response scores completed the study. At no time during the study were scores of 6 (vesicular eruption) or 7 (strong reaction spreading beyond test site) reported in any treatment group. While mild erythema was common across all study site visits, as might be expected with transdermal application, 77% of participants in the MTS group reported either no evidence (51.5%) or minimal evidence (25.5%) of irritation. Most participants in the OROS methylphenidate and placebo groups reported no evidence of irritation. In addition, across all 3 treatment conditions and all study site visits, 97.7% of participants reported no discomfort (87.3%) or minimal discomfort (10.4%), and 63.2% of participants had greater than

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Table 4. Most Frequently Reported Treatment-Emergent Adverse Events (≥ 5% in MTS and > 2 times placebo), Safety Population[a]

Adverse Event	MTS (N = 98)	OROS Methylphenidate (N = 91)	Placebo (N = 85)
Participants with ≥ 1 adverse event during the study	74 (75.5)	63 (69.2)	49 (57.6)
Decreased appetite	25 (25.5)	17 (18.7)	4 (4.7)
Insomnia	13 (13.3)	7 (7.7)	4 (4.7)
Nausea	12 (12.2)	7 (7.7)	2 (2.4)
Vomiting	10 (10.2)	9 (9.9)	4 (4.7)
Weight decreased	9 (9.2)	7 (7.7)	0 (0.0)
Tic	7 (7.1)	1 (1.1)	0 (0.0)
Affect lability	6 (6.1)	3 (3.3)	0 (0.0)
Nasal congestion	6 (6.1)	3 (3.3)	1 (1.2)
Anorexia	5 (5.1)	3 (3.3)	1 (1.2)
Nasopharyngitis	5 (5.1)	4 (4.4)	2 (2.4)

[a]Results shown as N (%) of participants reporting adverse events.
Abbreviations: MTS = methylphenidate transdermal system, OROS = osmotic-release oral system.

90% of the patch attached after 9 hours of wear. Two participants in the MTS group discontinued due to application site reactions and subsequently were successfully initiated and maintained on oral methylphenidate therapy without known evidence of systemic sensitization.

DISCUSSION

The primary objective of this 7-week, randomized, double-blinded, double-dummy, placebo-controlled, clinical trial was to evaluate the efficacy and safety of MTS compared to placebo, using OROS methylphenidate as a reference, for the treatment of ADHD in children in a naturalistic home and school setting. Overall, both MTS and OROS methylphenidate treatment resulted in similar significant improvements in behavior as rated by clinicians and teachers, compared with placebo. Additionally, analysis of the CPRS-R mean change from baseline by time of day (11:00 a.m. and 3:00 p.m.) demonstrated that parents witnessed improved ADHD symptoms with both MTS and OROS methylphenidate compared with placebo. Significant improvement in CPRS-R scores measured in the afternoon, approximately 8 hours after patch application, was observed with MTS treatment when compared with placebo ($p = .0001$). This result indicates that MTS provides effective symptom management throughout the school day and into the afternoon hours. Clinical trials that help to determine real-world use are advantageous, and in general, this trial allowed for practical dose titration similar to what may occur in a practical clinical setting.

The safety assessments conducted throughout the course of this study indicate that MTS is generally well tolerated. Concerns have grown over the cardiovascular risk of stimulant medications, including those used to treat ADHD.[27] However, in our study, no significant cardiovascular events related to treatment and no reports of serious adverse events or deaths were observed. Although small increases in mean systolic and diastolic blood pressure were noted in participants treated with MTS, there was no increase in the number of subjects with measurements above the normal range compared to baseline. Another area of concern with stimulant therapy is the prevalence of psychotic/manic events. One case of mild paranoia was reported during this trial in a participant receiving OROS methylphenidate. The event resolved without treatment or dose modification of study medication. Additionally, we did not observe clinically significant changes from baseline in ECG findings in the MTS group.

Clinical experience has demonstrated that the most common side effects associated with stimulant use in the treatment of ADHD generally resolve with continued treatment using optimized dosages. Approximately half of the participants enrolled in this trial were naive to ADHD treatment with a stimulant medication. The adverse events reported in this study are consistent with the results of previous studies of oral extended-release methylphenidate in pediatric patients, many of which did not include stimulant-naive participants.[28–31] Most participants also reported only minimal irritation at patch application sites. For the majority of participants, patch adhesion was excellent.

Tic disorder is a common occurrence in children with ADHD.[32] In this study, participants treated with MTS experienced a higher incidence of tics (N = 7, 7.1%; 9 events) as compared to participants treated with either OROS methylphenidate (N = 1, 1.1%; 1 event) or placebo (N = 0). In 7 additional clinical studies utilizing an MTS wear time range of 9 to 24 hours (2 included an OROS methylphenidate treatment arm and 4 were placebo controlled), the incidence of tics ranged from 1.0% to 8.3% (Pelham et al.[18,19] and data on file; Shire Development Inc.; Wayne, Pa.). One of these was a long-term, open-label MTS study with a wear time of 12 hours and a 1.0% incidence of tics. Across these 8 studies, the overall incidence of tics for MTS was similar to that for OROS methylphenidate (2.3% and 1.7%, respectively) (data on file; Shire Development Inc.; Wayne, Pa.). Taken together, this information suggests that this incidence rate most likely does not reflect a higher risk of tics associated with MTS usage.

The effects of stimulants on sleep behavior are unclear, and few published data report on sleep problems in relation to MTS. In this trial, insomnia was a commonly reported adverse event (13%, 8%, and 5% of MTS-, OROS methylphenidate–, and placebo-treated participants, respectively). Most cases resolved with continued study treatment, and there were no discontinuations due to insomnia. As evident by baseline CSHQ mean scores (range of 48 to 50 in all treatment groups), participants were within a childhood population norm (mean score,

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56.2 ± 8.9).[26] Throughout this study, CSHQ scores decreased in all study groups, as did the number of sleep items recorded as a problem. The incidence of spontaneously reported sleep problems in this trial did not correlate with the number of sleep problems when assessed using a targeted questionnaire (the CSHQ). These results suggest that treatment with MTS for ADHD had little effect on sleep habits.

Limitations

While this study was designed to evaluate the efficacy of MTS, it was not designed to specifically characterize the duration of treatment effect. The time course of treatment effect for MTS has been previously established in a laboratory classroom study.[20] In addition, the study was of relatively short duration, making it difficult to determine the long-term effects of treatment with MTS. Longer term studies are necessary to elucidate whether continued benefit of treatment occurs with MTS over an extended period of time. Finally, this study was not powered to compare the 2 active drug delivery systems, urging caution in any attempted comparison from these data.

Clinical Implications

There are limitations to all medications and their formulations. For instance, with oral medications, the beneficial, as well as the adverse, effects may endure until complete systemic elimination. Oral medications deliver a fixed amount of active drug, making it more difficult to control the duration of effect. MTS could be a beneficial option for parents of children with ADHD, as it provides extended-release stimulant medication that may allow flexibility in altering the duration of action. Further studies to investigate this potential use are needed.

CONCLUSION

The results of this study indicate that MTS is generally well tolerated and efficacious as acute therapy for the management of ADHD. MTS provides children with ADHD, and their parents, a new treatment option.

Drug names: atomoxetine (Strattera), clonidine (Catapres, Duraclon, and others), methylphenidate transdermal system (Daytrana), osmotic-release oral system methylphenidate (Concerta).

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